Germline Testing in Patients with Breast Cancer

ASCO-SSO Guideline

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Overview

1. Background & Methodology
   - Introduction
   - ASCO Guideline Development Methodology
   - Clinical Questions
   - Target Population and Audience
2. Summary of Recommendations
3. Discussion
   - Patient and Clinician Communication
   - Health Disparities
   - Additional Resources
   - Expert Panel Members

1 Background & Methodology

Introduction

- The advent of next-generation sequencing and multigene panel testing has changed the landscape of germline mutation testing with valuable implications for both prevention (particularly surgical) and treatment.
- Although the rapid expansion of genetic testing and the complexities of test interpretation have increased the imperative for appropriate patient education, the traditional pre- and post-test counseling model clearly is not sustainable given the substantial number of patients that will qualify for testing and the shortage in genetics counselors nationally.
- This ASCO-SSO clinical practice guideline provides clinicians and other health care practitioners, nurses and social workers, patients, genetic counselors, and caregivers with formal consensus-based recommendations regarding the role of germline mutation testing in patients with breast cancer based on the best available evidence.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  - a systematic literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO EBMC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Questions

This clinical practice guideline addresses five clinical questions:

1. Should clinicians offer *BRCA1/2* testing to all patients with newly diagnosed breast cancer?
2. Should all people with recurrent disease, local or metastatic, or with second breast primary, be offered *BRCA1/2* testing?
3. Should people with a personal history of breast cancer (and no active disease) be offered *BRCA1/2* testing?
4. What is the value of testing patients with a diagnosis of breast cancer for breast cancer predisposition genes other than *BRCA1/2*?
5. How should patients with breast cancer considering genetic testing be counseled?

Target Population and Audience

Target Population

- Patients with breast cancer and their families.

Target Audience

- Medical oncologists, radiation oncologists, surgical oncologists, medical geneticists, oncology nurses, patients, caregivers, oncology advanced practice providers, genetic counselors.

2 Summary of Recommendations

Summary of Recommendations

Clinical Question 1

- Should clinicians offer *BRCA1/2* testing to all patients with newly diagnosed breast cancer?

Recommendation 1.1

- All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are 65 years of age or younger at diagnosis should be offered *BRCA1/2* testing.

Formal Consensus

Agreement
87.50%

Summary of Recommendations

Recommendation 1.2

Formal Consensus

Agreement
92.50%

- All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are older than age 65 should be offered *BRCA1/2* testing if:
  - they are candidates for PARP inhibitor therapy for early-stage or metastatic disease,
  - they have triple-negative breast cancer,
  - their personal or family history suggests the possibility of a pathogenic variant,
  - they were assigned male sex at birth,
  - they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations.

Summary of Recommendations

Recommendation 1.3

Formal Consensus

Agreement
90.00%

- Patients undergoing *BRCA1/2* testing should also be offered testing for other cancer predisposition genes as suggested by their personal or family history. Consultation with a provider experienced in clinical cancer genetics can help guide this decision-making and should be made available to patients when possible.

Summary of Recommendations

Clinical Question 2

- Should all people with recurrent disease, local or metastatic, or with second breast primary, be offered *BRCA1/2* testing?

Recommendation 2.1

Formal Consensus

Agreement
97.50%

- All patients with recurrent breast cancer (local or metastatic) who are candidates for PARP inhibitor therapy should be offered *BRCA1/2* testing regardless of family history.

Qualifying Statement: Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in women with metastatic breast cancer and germline pathogenic variants in PALB2*.*

Summary of Recommendations

Recommendation 2.2

- *BRCA1/2* testing should be offered to patients with a second primary cancer either in the contralateral or ipsilateral breast.

Formal Consensus

Agreement
89.74%

Summary of Recommendations

Clinical Question 3

- Should people with a personal history of breast cancer (and no active disease) be offered *BRCA1/2* testing?

Recommendation 3.1

- All patients with a personal history of breast cancer diagnosed at 65 years or younger who are without active disease should be offered *BRCA1/2* testing if the result will inform personal risk management or family risk assessment.

Formal Consensus

Agreement
90.00%

Summary of Recommendations

Recommendation 3.2

Formal Consensus

Agreement
94.87%

- All patients with a personal history of breast cancer diagnosed over age 65 with no active disease, who meet one of the following criteria, should be offered *BRCA1/2* testing if the result will inform personal risk management or family risk assessment:
  - their personal or family history suggests the possibility of a pathogenic variant,
  - they were assigned male sex at birth,
  - they had triple-negative breast cancer,
  - they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations.

Summary of Recommendations

Clinical Question 4

- What is the value of testing patients with a diagnosis of breast cancer for breast cancer predisposition genes other than *BRCA1/2*?

Recommendation 4.1

- Testing for high penetrance genes beyond *BRCA1/2*, including *PALB2*, *TP53*, *PTEN*, *STK11*, and *CDH1*, could inform medical therapy, influence surgical decision making, refine estimates of risks of second primary cancer, and inform family risk assessment, and thus should be offered to appropriate patients.

Formal Consensus

Agreement
92.31%

Summary of Recommendations

Recommendation 4.2

Formal Consensus

Agreement
87.50%

- Testing for moderate penetrance breast cancer genes currently offers no benefits for treatment of the index breast cancer but may inform risks of second primary cancer or family risk assessment, and thus may be offered to appropriate patients who are undergoing *BRCA1/2* testing.

Recommendation 4.3

Formal Consensus

Agreement
91.43%

- If a multi-gene panel is ordered, the specific panel chosen should take into account the patient's personal and family history. Consultation with a provider experienced in clinical cancer genetics can be helpful in selecting a specific multi-gene panel or interpreting its results and should be made available to patients when possible.

Summary of Recommendations

Clinical Question 5

- How should patients with breast cancer considering genetic testing be counseled?

Recommendation 5.1

- Patients undergoing genetic testing should be given sufficient information before testing to provide informed consent.

Formal Consensus

Agreement
94.87%

Summary of Recommendations

Recommendation 5.2

Formal Consensus

Agreement
95.00%

- Patients with pathogenic variants should be provided with individualized post-test genetic counseling and offered referral to a provider experienced in clinical cancer genetics.

Recommendation 5.3

Formal Consensus

Agreement
88.57%

- Variants of uncertain significance should not alter management. Patients should be made aware that variants of uncertain significance may be reclassified as being pathogenic, and they should understand that periodic follow up is necessary. Consultation with a provider experienced in clinical cancer genetics can be helpful and should be made available to patients when possible.

Summary of Recommendations

Recommendation 5.4

Formal Consensus

Agreement
90.00%

- Patients without a pathogenic variant on genetic testing may still benefit from counseling, if there is a significant family history of cancer, and referral to a provider experienced in clinical cancer genetics is recommended.

3 Discussion

Patient and Clinician Communication

- ASCO has long underscored the primacy of informed consent for germline genetic testing.[1-3]
- Education about germline genetic testing should address, among other issues:
  - the purpose of germline testing
  - the genes being tested
  - the possible results of germline genetic testing (pathogenic or likely pathogenic variants, negative, VUS)
  - what the results may mean for medical management; to whom the test results will be returned
  - the implications of testing for family members
  - legal and confidentiality concerns, including discrimination by health insurers or employers.

Patient and Clinician Communication

- The most critical aspects of pretest genetic counseling (informed consent) and posttest genetic counseling (disclosure of results) are detailed in the guideline, along with key communication strategies and recommendations for patients with VUS.
- Communication around VUS should emphasize that VUS are increasingly common with the advent of multi-gene panels; may require follow up; and may later be reclassified.
- The results of testing can occasion or exacerbate a range of feelings among patients and family members, including anxiety, distress about the future, guilt, fear, anxiety, and worry,[4] which clinicians should acknowledge and respond to empathically in the context of a shared decision-making approach.[5,6]

Health Disparities

- A unique challenge in germline genetic testing is the unequal distribution of VUS.
- These ambiguous results are more frequent among racial and ethnic groups who have received less testing of a particular gene or genes, and for whom the normal range of genetic variability is less well-mapped.[7,8]
- A testing access disparity perpetuates a disparity in the clarity of genetic information.
- Population-based studies have documented a widening racial and ethnic gap in VUS results, which has been exacerbated by the trend toward sequencing many more genes.[9,10]
- Efforts to expand genetic testing access among clinically indicated patients are crucial to reduce the unequal burden of uncertain results on non-White patients.
- Awareness of these disparities in access to care should be considered in the context of this guideline, and providers should strive to deliver the highest level of cancer care to these vulnerable populations.

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines

- Patient information is available at www.cancer.net

Guideline Panel Members

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Abbreviations

- ASCO, American Society of Clinical Oncology
- PARP, poly(ADP-ribose) polymerase
- PGIN, Practice Guidelines Implementation Network
- SSO, Society of Surgical Oncology
- VUS, variants of uncertain significance

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